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Note

2-Phenyl-3-(2-aminobenzamido)quinazolin-4 (3*H*)-one as a synthon for bisazaheterocyclics

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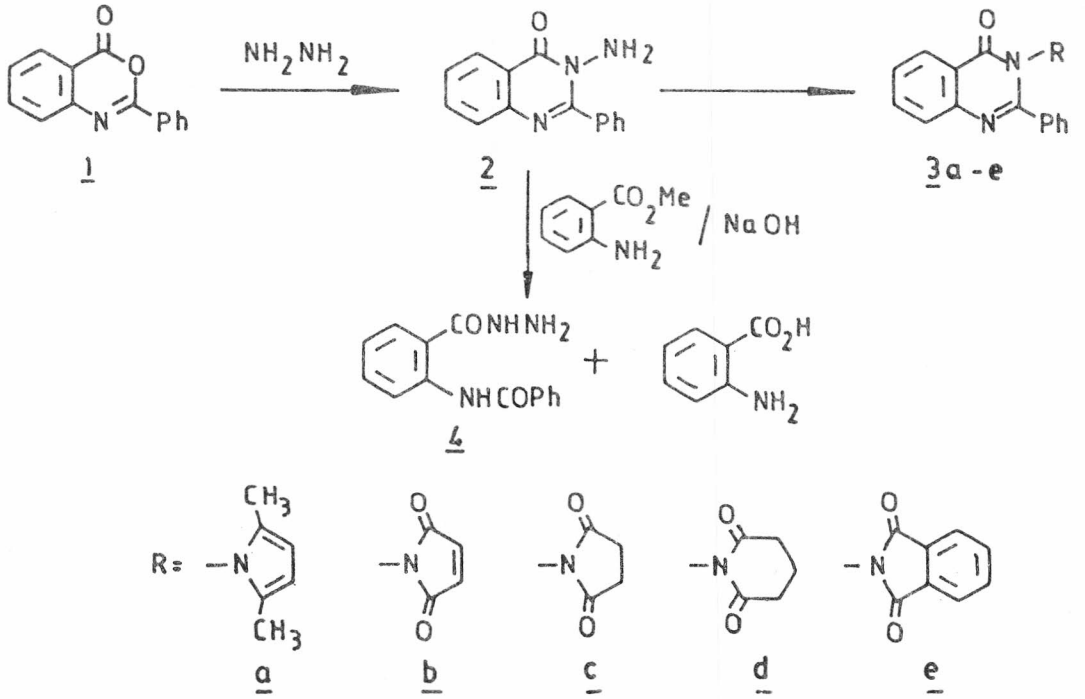
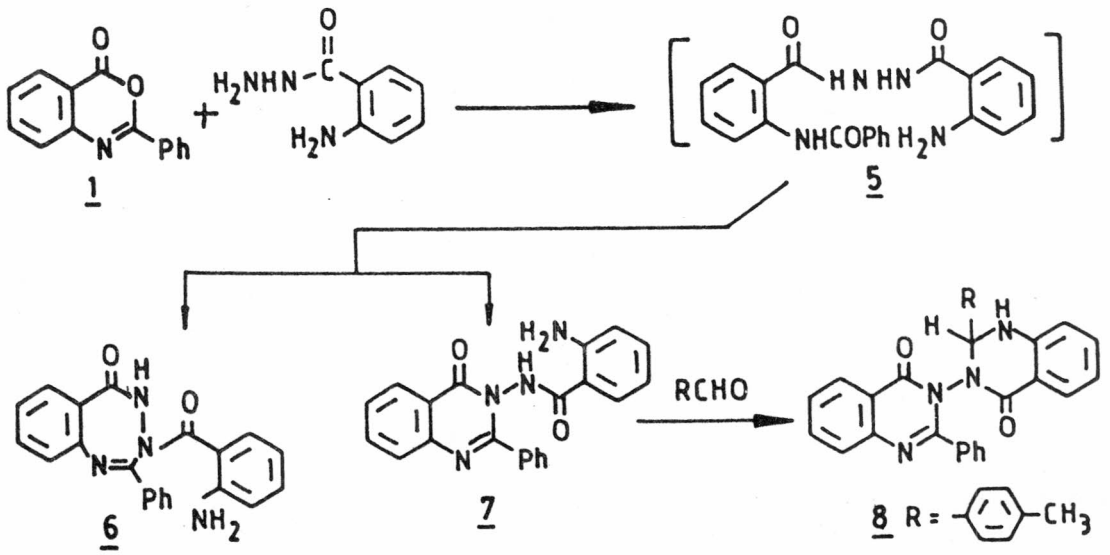
Synthesis of 2-phenyl-3-(2-aminobenzamido)-quinazolin-4(3*H*)-one **7**, a synthon of unsymmetrical bisazaheterocyclics, is reported from 3-amino-2-phenylquinazolin-4(3*H*)-one **2**. In an alternate synthetic route **7** has been prepared by refluxing 2-aminobenzoylhydrazine and 2-phenyl-3,1-benzoxazin-4(*H*)-one **1** in pyridine.

In continuation of our studies on bisazaheterocyclics as precursors for nitrogen centred free radicals[1], we report herein the synthesis of a versatile synthon, 2-phenyl-3(2-aminobenzamido)quinazolin-4(3*H*)-one **7**, of N, N-linked bisquinazolinones. A convenient scheme for obtaining **7** apparently involves benzoylation of 3-amino-2-phenylquinazolin-4(3*H*)-one **2** with 2-nitrobenzoyl chloride followed by nitro group reduction. The starting compound **2** was easily prepared from 2-phenyl-3,1-benzoxazin-4(*H*)-one **1** and hydrazine hydrate by a known procedure[2], and was characterised by derivatisation with 4-methoxybenzaldehyde[3], acetonyl acetone and anhydrides. Incidentally, the pyrrolyl and imidyl derivatives **3**, obtained in these reactions, have N-N linkage in the structure, and hence qualify as mixed azaheterocyclics. They could be a good source of quinazolinonyl radicals. Attempts to convert **2** to **7** by reacting with a benzene solution of *o*-nirobenzoyl chloride did not succeed. Reaction of **2** with methyl anthranilate in alkaline medium, opened up the quinazolinone ring to form the acyclic 2-benzoylamino benzoylhydrazine **4**[2] (Scheme I). Anthranilic acid[4] was also isolated from the reaction mixture as a co-product. Obviously, methyl anthranilate is undergoing alkaline hydrolysis during the reaction.

As an alternate synthetic route for **7**,2-aminobenzoylhydrazine and 2-phenyl-3,1-benzoxazin-4(*H*)-one **1** were refluxed in pyridine when 2-phenyl-3-(2-aminobenzamido)-1, 3, 4-benzotriazepin-5-one **6**, and its isomer, 2-phenyl-3-(2-aminobenzamido)quinazolin-4(3*H*)-one **7** (vide spectra) were obtained. This reaction gains importance



Scheme I



Scheme II

due to the fact that both quinazolinone (amino insertion) and 1,3,4-benzotriazepinone (hydrazine insertion) products are formed in one-pot, possibly through the intermediate **5**. 4-Methylbenzaldehyde reacted with **7** to yield 2-phenyl-3-(2-*p*-methylphenyl-1, 2-dihydro-4-oxo-quinazolin-3-yl)quinazolin-4(3*H*)-one **8** (Scheme II).

Work is in progress to synthesise N,N-linked mixed azaheterocyclics from **7**.

Experimental Section

All melting points reported are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on Perkin-Elmer 283 spectrophotometer using KBr, PMR spectra on Brucker (300 MHz) spectrometer (and chemical shifts in δ, ppm) using TMS as internal standard and mass spectra on Perkin-Elmer Hitachi RMU-6L instrument.

Reaction of 3-amino-2-phenylquinazolin-4(3*H*)-one 2 with acetonyl acetone. A mixture of **2** (0.5 g), and acetonyl acetone (0.3 mL) in acetic acid (10 mL) was heated on steam bath for 20 hr. The reaction mixture was then cooled and poured into 50 mL of ice-cold water. The solid separated was filtered, dried and passed through alumina (200 mesh) column using 9:1 benzene-pet.ether as eluent to isolate 2-phenyl-3-(2,5-dimethylpyrrol-1-yl)quinazolin-4(3*H*)-one **3a**. It was recrystallised from ethanol, m.p. 144°C; yield 80%; MS (Int. %): m/z 315(M^+,70), 273(13), 222(31), 119(97), 94(100), 90(19); IR (KBr): 1705 (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.98 (s, 6H, 2 × CH_3), 5.82 (s, 2H, −C=C-H), 7.3-8.39 (m,9H,Ar-H).

Reaction of 3-amino-2-phenylquinazolin-4(3*H*)-one 2 with anhydrides: General procedure. A solid mixture of **2** (0.5 g) and the appropriate anhydride (maleic, succinic, glutaric and phthalic anhydride, 3 mmol) was heated at 180 ± 10°C in an open ended test tube for 6 hr. The melt was resoldified by cooling the mixture, recrystallised from ethanol, and characterised as:

2-Phenyl-3-(maleimid-1-yl)quinazolin-4(3H)-one 3b, m.p. 168°C; yield 79%; MS (Int. %): m/z 317(M^+,52), 218(42), 179(24), 125(100), 77(89); IR (KBr): 1785, 1740, 1703 (C=O); ^{1}H-NMR ($CDCl_3$) δ (ppm) : 6.8 (s, 2H, −CH=CH−), 7.32-8.25 (m,9H,Ar-H).

2-Phenyl-3-(succinimid-1-yl)quinazolin-4(3*H*)-one 3c, m.p. 187°C; yield 78%; MS (Int. %): m/z 319 (M^+, 100), 264(58), 179(40), 119(22), 76(46); IR (KBr): 1780, 1740, 1703 (C=O); ^{1}H-NMR ($CDCl_3$): δ 2.45-2.95 (m,4H, $-CH_2-CH_2$), 7.35-8.27 (m,9H,Ar-H).

2-Phenyl-3-(glutarimid-1-yl)quinazolin-4(3*H*)-one 3d, m.p. 246°C; yield 74%; MS (Int. %): m/z 333(M^+,30), 149(45), 122(20), 105(15), 43(100); IR (KBr): 1762, 1722, 1700 (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.9-2.15 (m,2H,imidyl CH_2), 2.45-2.92 (m,4H,imidyl-CO-CH_2); 7.45-8.32(m,9H,Ar-H).

2-Phenyl-3-phthalimid-1-yl)quinazolin-4(3H)-one 3e, m.p. 174°C; yield 80%; MS (Int. %): m/z 367(M^+,100), 350(22), 322(15), 220(20), 179(27), 119(24); IR (KBr): 1790, 1740, 1703 (C=O); ^{1}H-NMR ($CDCl_3$): δ 7.27-8.00 (m,12H,Ar-H), 8.39 (d,1H, Ar-H, peri proton) respectively.

Reaction of 3-amino-2-phenylquinazolin-4(3*H*)-one 2 with methyl anthranilate. A mixture of **2** (300 mg), methyl anthranilate (1 mL) and so-

dium hydroxide (0.5 g) in ethanol (50 mL) was refluxed on water bath. After 2 hr, the solvent was distilled off and 10 mL of water was added and the solution neutralised carefully with hydrochloric acid. The aq. solution was extracted with chloroform (3 × 15 mL), and chloroform extract dried over anhyd. sodium sulphate. The solvent was distilled off and the solid obtained was passed through an alumina (200 mesh) column using benzene-ethyl acetate mixture as eluent to isolate 2-benzoylamino benzoylhydrazine **4** (9:1 benzene-ethyl acetate) in 52% yield and anthranilic acid (350 mg) (8:2 benzene-ethyl acetate), m.p. 147°C.

Reaction of 2-phenyl-3, 1-benzoxazine-4(*H*)-one 1 with 2-aminobenzoylhydrazine. A mixture of **1** (2.23 g) and 2-aminobenzoylhydrazine (1.5 g) in dry pyridine (50 mL) was refluxed for 6 hr. Pyridine was removed *in vacuo* and the residue was poured in ice-cold water (100 mL) containing 5 mL of hydrochloric acid (to remove traces of pyridine, if any). White coloured solid separated out, filtered, washed with water (2 × 20 mL) and passed through an alumina (200 mesh) column using benzene-ethyl acetate mixture as eluent to isolate 2-phenyl-3-(2-aminobenzamido)-1,3,4-benzotriazepin-5-one (**6**, 9:1 benzene-ethyl acetate), recrystallised from ethanol, m.p. 168°C; yield 28 %; MS (Int. %) m/z 237(100), 180(30), 120(67), 92(24), 77(33); IR (KBr): 3425, 3326 (NH_2), 3202 (−CO−NH), 1707, 1680 (C=O); ^{1}H-NMR ($CDCl_3$): δ 5.9 (br, 2H, NH_2), 6.7-8.2 (m,13H,Ar-H) and 2-phenyl-3-(2-aminobenzamido)quinazolin-4(3*H*)-one (**7**, 8:2 benzene-ethyl acetate), recrystallised from ethanol, m.p. 210°C; yield 72 %; MS (Int. %): m/z 357(M+1,10), 120(100), 92(15), 69(15), 43(10); IR (KBr): 3464, 3346 (NH_2), 3224 (−CO−NH), 1701, 1665 (C=O); ^{1}H-NMR (DMSO-d_6): δ 5.9 (s 2H, NH_2), 6.5-8.3 (m,13H,Ar-H), 11.1 (s, 1H, CO-NH).

Reaction of 2-phenyl-3-(2-aminobenzamido)quinazolin-4(3H)-one 7 with 4-methylbenzaldehyde. A mixture of **7** (0.1 g), 4-methylbenzaldehyde (0.2 mL) and acetic acid (1 mL) in methanol (10 mL) was refluxed for 4 hr. On standing for 1 hr, 2-phenyl-3-(2-*p*-methylphenyl-1,2-dihydro-4-oxo-quinazolin-3-yl)quinazolin-4(3*H*)-one **8** separated out from the reaction mixture which was filtered and recrystallised from ethanol, m.p. 255°C; yield 85 %; MS (Int. %): m/z 456 (M-2, 3), 237(100), 236(37), 222(48), 119(50); IR (KBr): 3346 (NH), 1704, 1661 (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.2 (s, 3H, CH_3), 5.5 (s,1H,NH), 6.4 (s, 1H, C-H), 6.6-8.2 (m, 17H, Ar-H).

References

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